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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
ARCHIE, NINA	

ART UNIT	PAPER NUMBER
1645	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/585,721	DUBREMETZ ET AL.	
	Examiner	Art Unit	
	Nina A. Archie	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 June 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4 and 6-9* is/are pending in the application.

4a) Of the above claim(s) *4,7 and 8* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *6* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on June 21, 2010 has been entered.

Amendment Entry

2. The amendment filed June, 28, 2010 has been entered. Claims 1 and 4 and 7-8 have been amended. Claims 1, 4, and 6-9 are pending. Claims 4 and 7-8 are withdrawn from consideration. Claims 1, 6, and 9 are under examination.

Election/Restriction

3. **Applicant argues**:

Applicants assert that the Office Action fails to explain why the inventions are independent and distinct. Applicants respectfully remind the Office that there must be an explanation as to why the inventions are separate and distinct, and it must be demonstrated that there would be a serious burden on the Examiner if a restriction were not made. Applicants assert that the Office Action fails to demonstrate either of the required elements and in particular, the Office Action fails to explain why the product claim of claim 1 is independent and distinct from the product claim of claim 9. Applicants respectfully request at least rejoinder of claim 9 to claims 1 and 6. Applicants request that the Examiner indicate that claims 4, 7 and 8 are eligible for rejoinder. Applicants assert that claim 4 is a process claim related to claims 1 and 6 as a product and method of use. Applicants state upon indication that the product claim is allowable, Applicants assert that at least claim 4, and possibly claims 7 and 8, be rejoined and deemed allowable provided that the claims contains all the elements of the allowed product claims. Applicants respectfully request notification of possible rejoinder of claims 4, 7 and 8 to claims 1 and 6.

Examiner's Response to Applicants Arguments:

Examiner agrees with Applicants' response in regards to claim 9. However as stated in the previous office action, claim 4 is directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: Original claims filed on 7/12/2006 are drawn to a product and the amended claims filed on 9/17/2009 are drawn to a method. Applicant has constructively elected invention on 7/12/2006 drawn to a product.

The action on the merits on 4/17/2009 of the instant application has been examined.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 4 and 7-8 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Grounds of Priority Maintained

4. Applicants state a certified copy of the priority document will be provided in due course. Therefore, the acknowledgment is made of applicant's claim for foreign priority based on application filed on 7/12/2006, however, that applicant has not filed a certified copy of the application as required by 35 U.S.C. 119(b). Moreover, Applicant is reminded that in order for a patent issuing on the instant application to obtain the benefit of priority the priority date is based on the priority document FRANCE 04 00260 filed 1/13/2004. Therefore should applicant desire to obtain the benefit of foreign priority under 35 U.S.C. 119(a)-(d) prior to declaration of interference, a translation of the foreign application should be submitted under 37 CFR 1.55 in reply to this application. Therefore, the effective (priority) date of the in the instant application is 1/13/2005.

Withdrawal of Rejection

5. The rejection of claims 1 and 6 under 35 U.S.C. 103(a) as being unpatentable over Meissner et al 2002 Journal of Cell Science 115 pgs. 563-574 has been withdrawn in view of applicant's amendments and arguments.

Response to Arguments

6. Applicant's arguments with respect to claims 1 and 6 have been considered but are moot in view of the rejections in the previous office action.

Claim Rejections Maintained

35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. The rejection of claim 6 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement are maintained for the reasons set forth in the previous office action. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicants arguments filed in response to the 35 U.S.C. 112 first paragraph, June 21, 2010 is carefully considered, but not found to be persuasive for the reasons below.

Applicant argues:

A) Applicants argue the three major genotypes are known for T. gondii strains: types I, II and III, whereby type I strains are characterized by an important virulence in mice. Applicants argue cysts, however, are rarely if ever developed from this strain type. Type II strains, on the other hand, are avirulent. Applicants argue an infection a type II strain can lead to death during the acute phase only at a high dosage or if mice have an increased sensibility to acute infection. Type II strains are responsible for the chronic phase of toxoplasmosis. Type III strains comprise both avirulent and intermediately virulent strains. Applicants argue the Examples in the present application, the RH strain that is used as the vaccine strain is a type I strain, whereas strains 76K and PRU, used are used as the challenge strains, are type II. Applicants argue the application expressly demonstrates that the vaccine obtained from a type I strain provides cross protection

against infections with type II strains. Applicants argue the application provides experimental results on mice (Example 4) and ewes (Example 5), wherein example 4 discloses vaccination of mice infected with type II strain 76K and example 5 discloses vaccination of ewes infected with type II strain PRU. Applicants argue one skilled in the art would recognize that the criterion to be measured is brain cysts number and given that type I strains rarely, if ever, result in cyst formation, infection with a type II T. gondii strain is ideal for use in challenge experiments. Applicants argue strain 76K is for example usually used in mice(see for instance Debard et al. (Infect. Immun. 1996 Jun, 64(6):2158-66; copy here enclosed), wherein strain 76K was used as a challenge strain to study immunization with a specific product association in mice measuring the amount of brain cysts in order to evaluate the protection of mice against infection with T. gondii, which is identical to Example 4, and concluded that this association allowed protection against chronic toxoplasmosis. Applicants argue Example 4 clearly demonstrates effective vaccination of mice with a vaccine obtained from a mutant type I strain against infection by a type II strain. Applicants state one skilled in the art would know that the criteria to be measured are abortions and lamb deaths rate (see for instance Dubey (Vet. parasit. 2009; 163: 1-14; copy here enclosed), in particular paragraph 3.1 (page 9) and Table 5), wherein ewes are inoculated orally with oocysts and infection with toxoplasmosis is evaluated by measuring fever, abortion and lamb death, identical to Example 5, thus Example 5 would confirm to one of skill in the art that effective vaccination of ewes with a vaccine obtained from a mutant type I strain against infection by a type II strain because the results in Example 5 are consistent with the mouse experiment results of Example 4. Applicants argue all abortions, whether febrile or infectious, can reasonably be assumed to be due to infection with toxoplasmosis, thus fewer abortions

(febrile + infectious) were seen in vaccinated ewes in Example 5 is proof that vaccination with the mic1-3KO strain is an efficient form of protection. Applicants argue type II strains are predominant in sheep and human toxoplasmosis, as reported in Owen et aL (J. Parasitol. 1999 Apr.; 85(2): 382-4; abstract here enclosed) and Ajzenberg et aL (J. Infect. Dis. 2002; 186: 684-9; copyhere enclosed), respectively. Applicants argue one person having ordinary skill in the art would have no reason to doubt that the vaccine of the invention is an efficient vaccine, in particular for humans and sheep.

Examiner's Response to Applicants arguements:

In regards to Point (A), the specification discloses micl-3KO mutant and the challenge step of mice immunized with the mic1-3KO mutant and the re-infection with the Toxoplasma gondii strain 76K which formed virtually no brain cysts (see page 26, lines 8-15). Therefore the specification is only limited a vaccine composition conferring "protection" using micl-3KO against infection by Toxoplasma gondii strain 76K but does not demonstrate protection against all Toxoplasma gondii strains utilizing a given mutant strain of *Toxoplasma gondii*. Furthermore the specification is also limited to the reduction of febrile abortions caused by *Toxoplasma gondii* through the administration of the mic1-3KO mutant, consequently, the data as set forth supra does not demonstrate that the composition confers "protection" but not prevention of infection by all Toxoplasma gondii. Therefore, one skilled in the art would not accept on its face the examples given in the specification as being correlative or representative of a successful model. Moreover, the specification as filed fails to provide particular guidance demonstrating a reasonable extrapolation which resolves the known unpredictability in the art for all *Toxoplasma gondii* provided in vivo in any and/or all organisms whereby prevention effects are provided in any

and/or all organisms. Moreover, the skilled artisan would clearly realize the critical deficiency of this specification with respect to the claim invention. Therefore a vaccine comprising type I mutant strain RH micl-3KO would not be effective on mice infected with type II strain 76K and on ewes infected with type II strain PRU. Moreover, one skilled in the art would not conclude that (1) the claimed vaccine would be effective against infection with any type of strain, hence the claimed vaccine would not be effective against infection with any type strain as the vaccine. Thus, Applicants responses aforementioned above are unpersuasive and the rejection is maintained.

As outlined previously, while being enabling for the reduction of febrile abortions caused by *T. gondii* through the administration of the mic1-3KO mutant does not provide enablement for any vaccine comprising any mutant strain of Toxoplasma gondii in which adhesion MIC1 and adhesion MIC3 are inactivated by deletion of each of MIC1 and MIC3 genes. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with the claimed invention.

Enablement is considered in view of the Wands factors (MPEP 2164.01 (A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary.

(A) The nature of the invention;

(B) The breadth of the claims;

(C) The state of the prior art;

(D) The level of one of ordinary skill;

(E) The level of predictability in the art;

(F) The amount of direction provided by the inventor;

(G) The existence of working examples; and

(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

Nature of the invention: The claims are drawn to a vaccine comprising a mutant strain of Toxoplasma gondii in which adhesion MIC1 and adhesion MIC3 are inactivated by deletion of each of MIC1 and MIC3 genes.

Breadth of the claims: The instant claims encompass protection against any of Toxoplasma gondii strain with a vaccine comprising a mutant strain of Toxoplasma gondii in which adhesion MIC1 and adhesion MIC3 are inactivated by deletion of each of MIC1 and MIC3 genes.

Guidance of the specification/The existence of working examples: The specification discloses, mice immunized with a mutant, wherein MIC1 and MIC3 were inactivated (mic1-3KO mutant) (see pg. 12 and Example 4). The specification discloses the mice form virtually no brain cyst during a reinfection with the Toxoplasma gondii strain 76K with a 99.9% protection. Therefore the data as set forth supra demonstrate that the vaccine composition confers "protection" using micl-3KO against infection by Toxoplasma gondii strain 76K but does not demonstrate protection against all Toxoplasma gondii strains. The specification discloses ewes immunized with mic1-3KO (see pgs. 28-30) and infected with oocysts of PRU strain at mid-gestation (see pg. 30 lines 20-30). Moreover, the specification discloses Tables 1-Table VI, on pages 33-37, which summarizes the results female ewes infected with oocysts of Prugniaud strain (PRU) at mid-gestation which show no febrile abortions occurred from ewes vaccinated with a mic1-3KO mutant strain, however the data disclosed in Tables II and V display the results of infectious abortions (see pg. 34 Table III and Table V pg. 37). Moreover, the specification states "that febrile abortions are abortions that are occur subsequently (at a later time) to a thermal peak which follows infection" (see pg. 32 line 35). Hence, the data as set forth supra demonstrate the reduction of febrile abortions due to the results of infectious abortions and the statement disclosed in the specification aforementioned above. Therefore, the specification is only limited to the reduction of febrile abortions caused by *Toxoplasma gondii* through the administration of the mic1-3KO mutant. Therefore the data as set forth supra does not demonstrate that the composition

confers "protection" against infection by Toxoplasma gondii. Moreover, there is no data regarding the induction of a protective immune response to a given pathogen was disclosed.

The data merely shows that said composition reduces the number of mice and ewes dying from Toxoplasma gondii. Furthermore the specification discloses data only for Toxoplasma gondii strain. Therefore, one skilled in the art would not accept on its face the examples given in the specification as being correlative or representative of a successful model. The working examples do not disclose any empirical data or results indicative of a vaccine comprising a mutant strain as claimed against infection by all Toxoplasma gondii strains.

The specification does not disclose any working example that the recited vaccine as claimed will work against infection by all Toxoplasma gondii strains with mic1-3KO. A vaccine by definition must provide protection against an infection demonstrable by challenge experiments. The specification is devoid of any teaching that the claimed vaccine against infection caused by any strain of Toxoplasma gondii discloses a protective response against any subject.

State of the art: Although many investigators have tried to develop vaccines based on specific antigens, it is well understood that the ability of an antigen to stimulate antibody production does not necessarily correlate with the ability of the antigen to stimulate an immune response capable of protecting an animal from infection (Chandrashekar et al., US Patent 6,248,329, col. 1, lines 35-41). It is well recognized in the vaccine art, that it is unclear whether an antigen derived from a pathogen will elicit protective immunity. Ellis (Chapter 29 of Vaccines, Plotkin, et al. (eds) WB Saunders, Philadelphia, 1998, especially p. 571, paragraph 2) exemplifies this problem in the recitation that "the key to the problem (of vaccine development) is the identification of that protein component of a virus or microbial pathogen that itself can elicit the production of protective antibodies.., and thus protect the host against attack by the pathogen." Moreover, protein chemistry is probably one of the most unpredictable areas of biotechnology. Consequently, the effects of sequence dissimilarities upon protein structure and function cannot be predicted. For the reasons set forth supra, the state of the art is has limitations to a vaccine composition and the state of the art is unpredictable with regard to the recited vaccine as claimed.

In conclusion, the claimed invention is not enabled for any vaccine against all Toxoplasma gondii comprising any mutant strain of Toxoplasma gondii in which adhesion MIC1 and adhesion MIC3 are inactivated by deletion of each of MIC1 and MIC3 genes. The instant claims encompass protection against any of Toxoplasma gondii strain with a vaccine comprising a mutant strain of Toxoplasma gondii in which adhesion MIC1 and adhesion MIC3 are inactivated by deletion of each of MIC1 and MIC3 genes. The state of the art teaches that there are limitations to the recited vaccine composition and the state of the art is unpredictable. In view of the lack of support in the art and specification for an effective vaccine, it would require undue experimentation on the part of the skilled artisan to make and use the vaccine as claimed; therefore the claims are not enabled. The specification is devoid of any teaching that the claimed vaccine against infection caused by any strain of Toxoplasma gondii discloses a protective response against any subject. As a result, for the reasons discussed above, it would require undue experimentation for one skilled in the art to use the claimed method.

Conclusion

7. Claims 1 and 9 are free of the art of record.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nina A. Archie whose telephone number is 571-272-9938. The examiner can normally be reached on Monday-Friday 8:30-5:00p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Nina A Archie
Examiner
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REM 3B31

/Robert A. Zeman/
for Nina Archie, Examiner of Art Unit 1645